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Lactate and lactylation: novel perspectives on fibrosis pathogenesis and therapeutic directions

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Abstract
Fibrosis is the common terminal pathway of abnormal tissue repair in various chronic diseases and has become a major global health challenge. Recent research has identified metabolic reprogramming as one of the key factors in the pathogenesis of fibrosis. Lactate, once considered a simple byproduct of glycolysis, has now been confirmed as a crucial metabolic messenger regulating intercellular communication and functional remodeling. The dynamic balance of intercellular lactate shuttling is essential for maintaining tissue homeostasis, and its dysregulation has been closely linked to the progression of fibrosis. Lactylation, a novel post-translational modification driven by lactate accumulation, can regulate protein function and gene expression, thereby playing a significant role in the pathogenesis of fibrosis. In this review, we summarize the latest advancements in the role of lactate and lactylation in the pathogenesis of fibrosis. By integrating the most recent research, we emphasize the importance of lactylation as a potential therapeutic target and explore the translational prospects of targeting lactate metabolism and lactylation in anti-fibrotic treatments, thereby providing novel insights for clinical intervention.

Keywords Lactate, Lactylation, Fibrosis

Introduction

Fibrosis is a pathological process triggered by chronic injury or persistent inflammatory stimulation, characterized primarily by the excessive secretion of extracellular matrix (ECM) by abnormally activated myofibroblasts, leading to abnormal tissue remodeling. Under normal circumstances, tissue function can be restored after repair, but repeated injury or dysregulated repair can result in excessive ECM deposition, causing normal tissue to be gradually replaced by fibrous tissue, thereby inducing fibrosis [1]. It is noteworthy that fibrosis is not an independent disease but rather a common pathological manifestation of various chronic diseases in their terminal stages [2–4]. Fibrosis-induced end-stage diseases impose a heavy burden on global health and have become a focal area in current medical research. However, satisfactory treatment methods are still lacking, largely because the pathogenesis and pathological pathways of fibrosis in different organs have not yet been fully elucidated. In recent years, with the rapid development of epigenetics and multi-omics technologies, scientists have made significant progress in unraveling the complex mechanisms of fibrosis. Emerging research indicates

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that the accumulation of lactate in the body and the post-translational modification (PTM) processes it triggers may play a crucial role in the pathogenesis of fibrosis.

Since its discovery in 1780, lactate has long been considered a waste product of anaerobic glycolysis. However, recent studies have confirmed that lactate is not only a product of glycolysis but also serves as an important signaling molecule involved in various pathophysiological processes such as gluconeogenesis, signal transduction, and immune modulation [5–8]. These findings have altered the traditional perception of lactate, transforming it from a metabolic waste product to a molecule with multiple physiological functions. As research into the functions of lactate has deepened, researchers have gradually discovered a new PTM related to lactate, namely lactylation [9]. An increasing body of evidence suggests that lactylation actively participates in a range of critical cellular physiological processes, including signal transduction, regulation of gene expression, metabolic control, and immune responses [10–13]. Moreover, lactylation is closely associated with the development of numerous diseases, such as cancer, cardiovascular diseases, kidney diseases, and neurodegenerative disorders [14–17]. The discovery of lactylation demonstrates the intricate relationship between genes, metabolism, and epigenetics, highlighting the potential of lactylation as a novel therapeutic target in the treatment of various diseases.

Although some previously published papers have reviewed the role of PTM in fibrosis across different organs [18–20], there is still a lack of perspective linking lactylation to fibrosis. This article systematically reviews the complex mechanisms of lactate and lactylation in fibrosis. We integrate the latest research on lactylation with the manifestations of fibrosis in various organs, aiming to unveil the intricate relationship between lactylation and fibrosis. We hope to further expand the in-depth understanding of the interrelationship between lactate, lactylation, and fibrosis, thereby providing new insights and theoretical foundations for intervention strategies in fibrosis-related diseases.

Lactate

The sources of lactate

For a long time, lactate was considered a metabolic waste product in organisms. Lactate in organisms primarily exists in two enantiomeric forms: L-lactate and D-lactate [21]. L-lactate is the predominant form in organisms and participates in various physiological processes, including glycolysis; D-lactate is present in lower concentrations, and its excessive accumulation may lead to health issues [22]. Glycolysis is the primary source of L-lactate. Under normal physiological conditions, glucose enters cells with the assistance of glucose transporters and is converted into pyruvate through the action of a series of glycolytic enzymes, including hexokinase. In the presence of sufficient oxygen, pyruvate enters the mitochondria and is converted into acetyl-CoA under the action of pyruvate dehydrogenase, subsequently participating in the tricarboxylic acid cycle (TCA) to generate ATP. In an oxygen-deficient environment, pyruvate is directly converted into lactate by lactate dehydrogenase (LDH) to provide energy [23]. Notably, the Warburg effect exists in tumor cells, where even in the presence of oxygen, cancer cells still tend to obtain energy by converting glucose into lactate [24]. This phenomenon has become one of the core areas of cancer metabolism research, and recent studies have found that the Warburg effect can promote DNA repair and tumor progression through lactylation [25]. However, it is worth emphasizing that a substantial body of research has confirmed the presence of the Warburg effect in non-tumor cells as well [26–28]. Moreover, considering the potential role of lactate and lactylation in fibrosis, it is plausible that the Warburg effect may also be involved in the occurrence and development of fibrosis through similar mechanisms, which could be a promising direction for future research.

Another significant source of L-lactate is the catabolism of glutamine, which is converted into α-ketoglutarate under the action of glutaminase and glutamate dehydrogenase, entering the TCA cycle. Through a series of enzymatic reactions, it is then transformed into pyruvate, which subsequently exits the mitochondria and is reduced to L-lactate in the cytoplasm, catalyzed by LDH [29]. The concentration of D-lactate in the body is relatively low and is typically produced from methylglyoxal (MGO) under the catalysis of glyoxalase 1 and 2 (GLO1&2) [30] (Fig. 1).

The transport of lactate

Monocarboxylate Transporter (MCT) is an important class of membrane transport proteins, belonging to the solute carrier superfamily, primarily responsible for the transmembrane transport of monocarboxylic acids such as lactate and pyruvate. To date, 14 types of MCTs have been identified, among which MCT1 and MCT4 have garnered significant attention due to their crucial roles in lactate transport [31]. MCT1 is widely expressed in various tissues, mainly responsible for lactate uptake, while MCT4 is highly expressed in tissues with active glycolysis, primarily responsible for lactate efflux [32]. In skeletal muscle cells, lactate can be exported via MCT4 and subsequently taken up by tissues such as the heart through MCT1, serving as an energy substrate to enter the TCA cycle for oxidative function [31]. However, studies have shown that under conditions of metabolic acidosis, MCT1 in the renal proximal tubule may be involved in lactate export, which is speculated to be related to its high affinity for lactate [33]. Additionally,

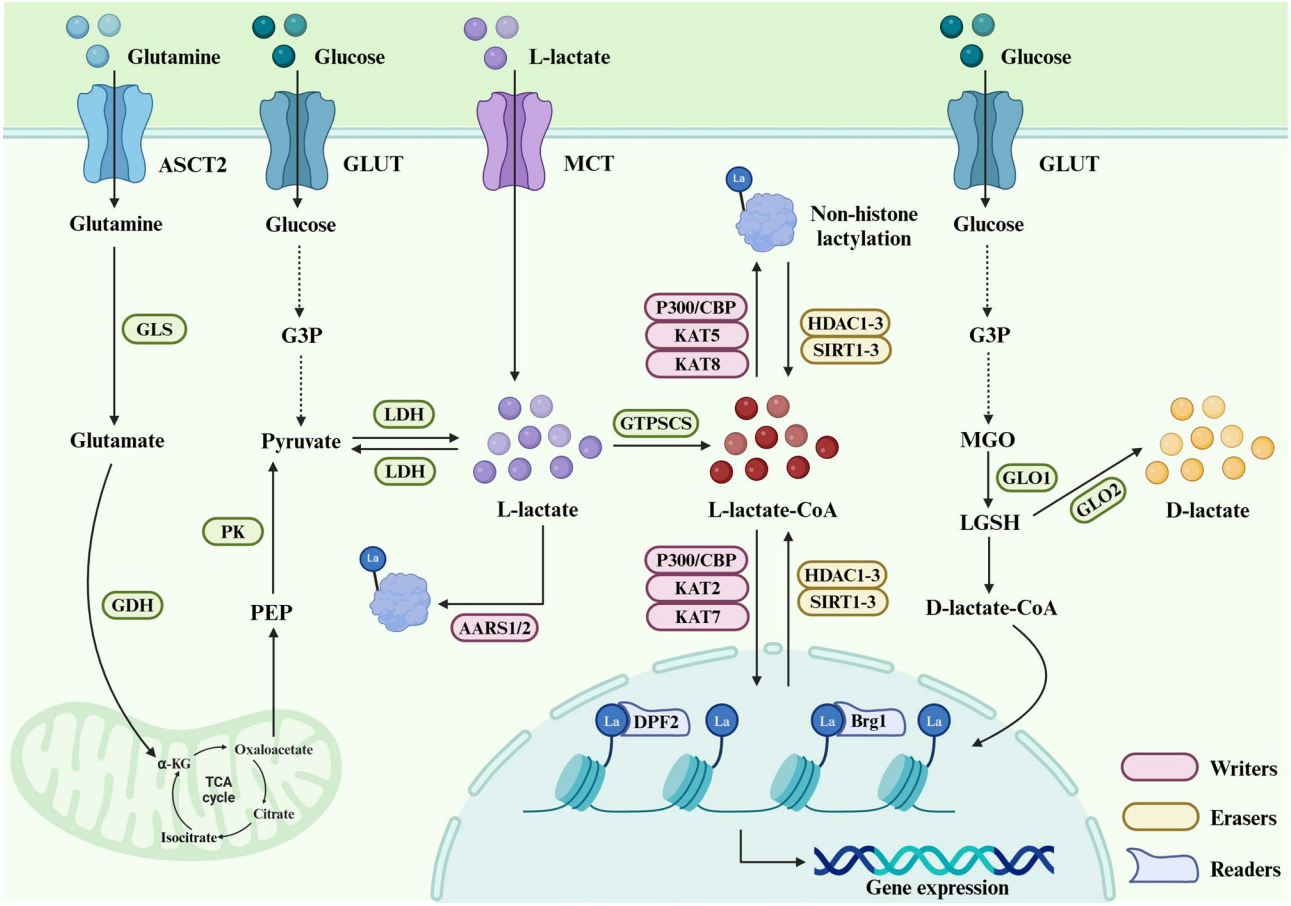

Fig. 1 Metabolic pathways of lactate production and lactylation modification. This schematic illustrates the major metabolic sources and downstream fates of L-lactate and D-lactate in cells. L-lactate is generated through glycolysis and glutaminolysis, while D-lactate is produced from LGSH under the enzymatic action of GLO2. Glycolysis is the primary source of L-lactate production, contributing significantly more lactate than glutaminolysis. L-lactate contributes to lactylation through two routes: directly mediating lactylation modification via ARRS or being converted into L-lactyl-CoA by GTPSCS, subsequently participating in histone and non-histone lactylation modifications regulated by writers and erasers to influence gene expression. Additionally, D-Lactyl-CoA generated by LGSH can participate in histone lactylation modification through a non-enzymatic mechanism. (Abbreviations: ARRS alanyl-tRNA synthase; ASCT2 alanine-serine-cysteine transporter 2; G3P glycerol 3-phosphate; CBP creb-binding protein; GDH glutamate dehydrogenase; GLO1&2 glyoxalase 1&2; GLS glutaminase; GLUT glucose transporters; GTPSCS guanosine triphosphate-specific SCS; HDAC1–3 histone deacetylases 1–3; KAT2&5&7&8 lysine acetyltransferase2&5&7&8; LDH lactate dehydrogenase; LGSH lactoylglutathione; MCT monocarboxylate transporter; MGO methylglyoxal; PK pyruvate kinase; SIRT1–3 sirtuins 1–3)

the upregulation of MCT expression was observed in parallel with increased lactylation under hyperglycemic conditions, suggesting a coordinated role in promoting fibrotic changes, although direct regulatory interactions remain to be clarified [34].

Lactylation

The discovery of lactylation

PTM influences gene expression through various mechanisms and precisely regulates protein functions, making it an important area of research in epigenetics. With the development of mass spectrometry-based proteomics, a variety of novel PTMs have been discovered, including glutarylation [35], crotonylation [36], and succinylation [37]. These PTMs regulate protein structure, thereby affecting cellular physiological activities. In 2019, Zhang et al. first reported a novel PTM, namely histone lysine lactylation (Kla), which quickly became a new research hotspot. They used high-performance liquid chromatography-tandem mass spectrometry technology to detect a mass shift on histones in MCF-7 cells. A metabolic experiment with ^{13}C3-labeled L-lactate confirmed that this shift originated from lactylation modification of lysine residues [9]. In subsequent studies, they further confirmed that L-lactate is the primary precursor of histone Kla [38]. It should be emphasized that lactylation is not limited to the specific protein histone; various signaling molecules and enzymes can also undergo lactylation [39–42]. Moreover, the regulation of histone Kla by lactate is actively driven by enhanced glycolysis and inhibited by mitochondrial oxidative phosphorylation.

The process of lactylation

The specific process of lactylation has not yet been fully elucidated. It is speculated that the process is likely an enzyme-catalyzed reaction similar to other acylation reactions, where lactyl-CoA serves as the lactate donor. Under the action of specific CoA transferases, the lactate group is transferred to the lysine residues of histones, forming lactylation modifications [9, 43]. Recent research on GTPSCS, a lactyl-CoA synthetase, has shed light on the source of lactyl-CoA [44]. However, no specific lactyltransferase has been identified so far. Therefore, it is hypothesized that the process is catalyzed by enzymes with acyltransferase activity, such as p300/CREB-binding protein C (CBP) [45]. Moreover, studies have confirmed that under the action of GLO1, the precursor of D-lactate, MGO, can combine with glutathione to form lactoylglutathione. LGSH can be non-enzymatically converted into D-lactyl-CoA, which then participates in histone lactylation within the cell nucleus. Additionally, under the catalysis of GLO2, LGSH can be decomposed into D-lactate and glutathione [46]. Notably, recent findings have revealed that AARS1/2 (an aminoacyl-tRNA synthetase) can catalyze the lactylation process without the involvement of lactyl-CoA [47, 48]. AARS1/2 can directly utilize free L-lactate as a substrate to generate the intermediate lactyl-AMP in an ATP-dependent manner, and subsequently transfer the lactyl group covalently to lysine residues on target proteins, thereby mediating lysine lactylation. (Fig. 1). This discovery provides a new perspective for understanding the mechanism of lactylation and may reveal a broader role of lactate in protein modification.

In epigenetics, most acylation modification processes are regulated by writers, erasers, and readers. Table 1 summarizes the currently discovered writers, erasers, and readers related to lactylation modification. Among them, writers refer to enzymes that can add acylation modifications to the lysine residues of histones. Zhang et al. have confirmed that P300 can act as a writer to participate in the lactylation modification process, catalyzing the lactylation of histones [9]. Subsequent studies have demonstrated that CBP, a homolog of P300,

Table 1 Regulatory enzymes of lactylation

Type	Enzyme	Organism	Target	Function	Ref
Writer	P300	Human, mice	H3K18	Catalyzes histone lactylation to boost M2-like gene expression	[9]
	CBP	Mice	HMGB1	Promotes the cytoplasmic accumulation of HMGB1 and exosomal secretion	[45]
	KAT2/GCN5	Mice	H3K18	Promotes the transcription of repair genes in macrophages	[49]
	KAT5/TIP60	Human	Vps34-K356/K781	Promotes the autophagic activity of skeletal muscle cells and tumor cells	[50]
	KAT7/HBO1/MYST2	Human	H3K9	Promotes gene expression in the transcription start site region	[51]
	KAT8	Human	eEF1A2-K408	Promotes protein synthesis and tumor cell proliferation	[103]
	AARS1	Human	p53-K120/K139	Inhibiting the tumor-suppressing function of p53 promotes tumorigenesis	[48]
	AARS2	Human, mice	cGAS-K131/K156	cGAS fails to bind DNA leading to suppression of the innate immune response	[47]
	YiaC	Escherichia coli	PykF-K382	Reduces the activity of PykF to slow down bacterial growth	[52]
	GNAT13	Streptococcus mutans	RpoA-Lys173	Inhibiting the synthesis of extracellular polysaccharides reduces biofilm formation	[53]
Reader	Brg1	Mice	H3K18	Promotes chromatin remodeling during the reprogramming process	[54]
	DPF2	Human	H3K14	Promotes the proliferation and survival of cancer cells	[55]
Eraser	HDAC1	Human	H3K18, H4K5	Regulates gene expression and maintains cellular homeostasis	[56]
	HDAC2	Human	H3K18, H4K5	Regulates gene expression and maintains cellular homeostasis	[56]
	HDAC3	Human	H3K18, H4K5	Regulates gene expression and maintains cellular homeostasis	[56]
	SIRT1	Human	Non-histone proteins (EGFP/fLuc)	Restores the function of proteins EGFP and fLuc	[104]
	SIRT2	Human	H3K18, H4K8, H4K12	Inhibits the proliferation and migration of neuroblastoma cells	[105]
	SIRT3	Human	H4K16, H3K9	Removes the H4K16la modification	[106]
	CobB	Escherichia coli	PykF-K382	Enhances the activity of PykF to promote bacterial growth	[52]

enhances the lactylation of HMGB1 in macrophages [45]. Recent research has further expanded the scope of lactylation writers: GCN5 has been confirmed to regulate the level of histone lactylation [49], and KAT5 has also been reported to potentially have the function of a lactylation writer [50]. Notably, Niu et al. discovered that HBO1 specifically catalyzes histone lactylation at the H3K9 site, and this modification is significantly enriched in the transcription start site region [51]. Lactylation has also been found in prokaryotes, with YiaC and GNAT13 identified as writers of lactylation in prokaryotes [52, 53].

Lactylation "reader" proteins are able to recognize and bind to lactylated sites, thereby regulating downstream biological functions. Hu et al. discovered that Brg1 may be a potential lactylation reader. They found that Dux promotes lactylation at the H3K18 site by recruiting P300, and that Brg1 has a significant interaction with H3K18 lactylation. This interaction can significantly enhance the efficiency of reprogramming [54]. On the other hand, Zhai et al., using a combination of multivalent photoaffinity probes and quantitative proteomics, discovered that DPF2 can bind to and interact with H3K14 lactylation [55].

Eraser proteins can restore the original conformation of modified proteins by removing lactyl groups. Moreno-Yruela et al. found that HDAC1-3 and SIRT1-3 play important roles in the removal of histone lactylation modifications, with HDAC1-3 showing high efficiency in removing various acylations [56]. Notably, the lactylation removal activity of HDAC3 is significantly higher than that of SIRT2, with an efficiency thousands of times greater than SIRT2 [57]. In prokaryotes, CobB has been found to act as an eraser to remove lactylation modifications, thereby restoring the original function of proteins [52].

The discovery of epigenetic enzymes involved in lactylation provides a new perspective for understanding the function of lactylation modifications in the regulation of gene transcription. However, it must be emphasized that the mechanisms of action of these lactylation-related regulatory factors and their functions in cellular physiological regulation have not yet been fully elucidated. Future research needs to further explore their recognition mechanisms and roles in cell fate determination to gain a deeper understanding of the biological significance of lactylation modifications.

Fibrosis driven by lactate

Lactate activation of fibrosis-related cells

During the progression of fibrosis, the formation of the ECM involves the coordinated participation of various fibrosis-related cells, including phenotypic transitions of fibroblasts, mesothelial cells, epithelial cells, endothelial cells, and pericytes [58–62]. Recent studies have revealed that lactate, as an important metabolic product, can drive the occurrence and development of fibrosis by activating these fibrosis-related cells (Fig. 2).

As the most common cell type in connective tissue, fibroblasts are the main cellular source of the myofibroblast pool in the progression of fibrosis in most organs [61]. During fibrosis, TGF-β acts as a key cytokine with important regulatory functions. Kottmann et al. confirmed that in primary human lung fibroblasts, lactate can activate the TGF-β signaling pathway in a pH-dependent manner, inducing the transformation of fibroblasts into myofibroblasts [63]. Subsequent studies found that gossypol, a specific inhibitor of LDH, can reduce lactate production and decrease the bioactivity of TGF-β by inhibiting LDH activity, thereby suppressing the differentiation of fibroblasts [58]. It is worth noting that lactate also has the ability to activate fibroblasts independently of the TGF-β signaling pathway, and it can effectively induce fibroblast activation on its own [64]. In addition, in bleomycin-induced pulmonary fibrosis mouse models lactate can promote glycolysis and lactate accumulation by activating pyruvate dehydrogenase kinase, upregulate the expression of fibrosis markers (such as α-SMA and COL1A1), and drive the activation of fibroblasts and the fibrotic process (Fig. 2A) [65].

The process by which epithelial cells lose polarity and acquire a mesenchymal phenotype is called epithelial-mesenchymal transition (EMT). The acidification of the extracellular microenvironment caused by lactate accumulation can activate TGF-β, inducing EMT in epithelial cells and thereby promoting the excessive secretion and abnormal deposition of the ECM [66]. It is worth noting that lactate can not only act alone but also synergize with TGF-β to further promote the occurrence of EMT and exacerbate the fibrotic process (Fig. 2A) [65]. Endothelial-mesenchymal transition (EndoMT) is the process by which endothelial cells transform into a mesenchymal cell phenotype. Xu et al. confirmed that in ischemic flap mouse models, lactate can promote the phosphorylation and nuclear translocation of the transcription factor Twist1, activate the TGF-β/Smad2 pathway, and thereby induce the occurrence of EndoMT, ultimately worsening the fibrotic process [67].

Lactate regulation of immune cell phenotypes

In addition to the aforementioned fibrosis-related cells, lactate can also play an important role in the fibrotic process by regulating the phenotypes and functions of immune cells. Macrophages are plastic and heterogeneous immune cells that can be simply divided into pro-inflammatory M1 or anti-inflammatory M2 types based on different microenvironmental signals [68]. Previous studies have shown that M1 macrophages promote ECM degradation by secreting pro-inflammatory cytokines

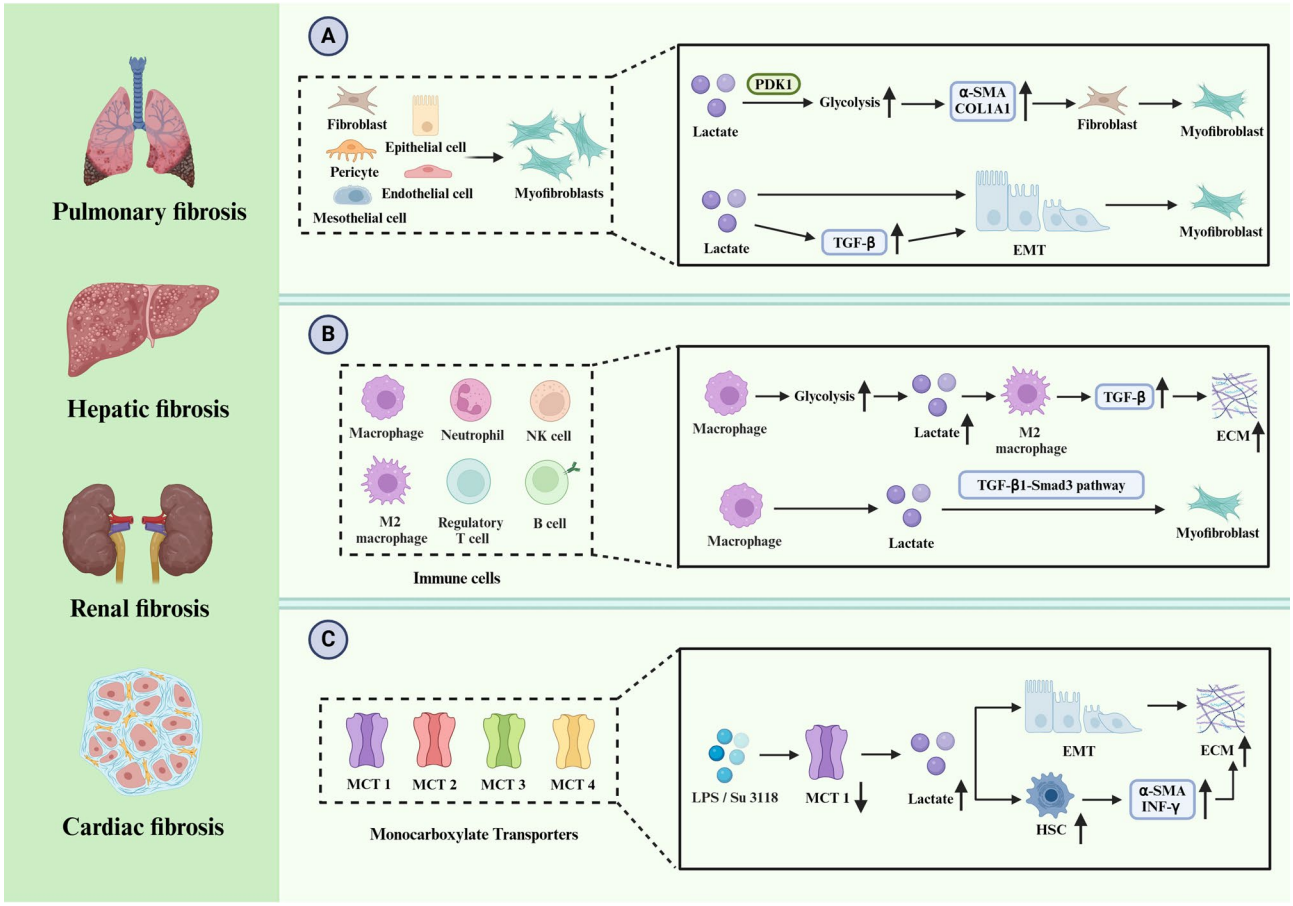

Fig. 2 Schematic of the molecular mechanisms of lactate involvement in fibrosis. Lactate contributes to fibrosis across multiple organs through the following pathways: (**A**) In the lung, lactate induces the differentiation of fibrosis-associated cells into myofibroblasts. (**B**) In the lung and kidney, lactate modulates the phenotypic polarization of immune cells, contributing to pro-fibrotic inflammation. (**C**) In the lung and liver, dysregulated lactate transport via MCTs leads to ECM deposition and fibrotic progression. (Abbreviations: COL1A1 collagen type I alpha 1 chain; ECM extracellular matrix; EMT epithelial-mesenchymal transition; HSC hepatic stellate cell; LPS lipopolysaccharide; MCT monocarboxylat transporter; PDK1 pyruvate dehydrogenase kinase 1; Su 3118 syrosingopine)

and inducing fibroblast activation through matrix metalloproteinases, whereas M2 macrophages facilitate TGF-β1-dependent fibroblast activation and collagen deposition [69–71]. In fibrotic mouse lungs, alveolar macrophages exhibit significant metabolic reprogramming, with enhanced glycolytic activity and lactate production. These metabolic changes lead mouse alveolar macrophages to differentiate towards an M2-like phenotype and promote abnormal ECM accumulation through the secretion of TGF-β1 (Fig. 2B) [72]. Notably, lactate not only acts as a metabolic product but also functions as a signaling molecule that directly acts on alveolar macrophages, upregulating profibrotic factors such as ARG1 and PDGFA, thereby exacerbating fibrosis progression [73]. Moreover, macrophages can transform into myofibroblasts via the lactate-induced TGF-β1-Smad3 pathway, leading to enhanced ECM deposition in mouse kidneys (Fig. 2B) [74]. A previous clinical study found that the lactate concentration in the bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis is positively correlated with the degree of neutrophil infiltration [75]. Further studies have shown that neutrophils can release the key profibrotic cytokine IL-17 [76], suggesting that lactate may participate in the fibrotic process by regulating the function of neutrophils. Meanwhile, in patients with myelofibrosis, elevated serum lactate levels can induce the proliferation of immunosuppressive cells such as regulatory T cells and monocytic myeloid-derived suppressor cells. These cells suppress the body's immune response, promote tumor cell immune escape, and ultimately lead to the progression of the fibrotic disease course [77].

MCT regulation of fibrosis

MCTs, as lactate transporters, play a crucial role in the fibrotic process. Lipopolysaccharide (LPS) can inhibit the expression of MCT1 in mouse alveolar epithelial cells, leading to extracellular lactate accumulation. This

accumulation triggers EMT in alveolar epithelial cells, ultimately promoting the formation of pulmonary fibrosis in LPS-injected mouse models (Fig. 2C). Overexpression of MCT1 can alleviate LPS-induced pulmonary fibrosis [66]. Similar findings were reported in another study, where inhibition of lactate transport via MCT activation led to the activation of human hepatic stellate cells (HSCs) in vitro and exacerbated liver fibrosis in mice, with upregulation of profibrotic gene expression and excessive deposition of the extracellular matrix (Fig. 2C) [78]. However, these conclusions were challenged by Huang et al., who found that upregulation of MCT1 increases lactate efflux, resulting in extracellular lactate accumulation, which activates HSCs and ultimately drives the occurrence and progression of hepatic fibrosis [79]. It is evident that the mechanisms by which lactate transport promotes fibrosis need to be further investigated. However, it can be affirmed that regulating lactate transport holds promise as a potential new direction for the treatment of fibrotic diseases.

Fibrosis driven by lactylation

Lactylation in hepatic fibrosis

HSCs play a central role in liver fibrosis [80]. Rho et al. were the first to demonstrate that lactylation drives the occurrence and progression of liver fibrosis in both mouse models and human liver tissues by regulating the activation and gene expression of HSCs, laying an important theoretical foundation for elucidating the mechanisms of lactylation in liver fibrosis. However, they did not clarify the specific mechanisms by which lactylation promotes liver fibrosis [81]. In subsequent studies, Wu et al. established both in vivo rat models and in vitro human HSC models, and found that H3K18 lactylation can promote the transcriptional activation of the SOX9 gene, thereby driving the activation of HSCs and the progression of liver fibrosis [82]. Notably, SOX9, as an important member of the SOX transcription factor family, has been shown to be involved in the pathological processes of fibrosis in various organs [60, 83, 84]. IGF2BP2, as a newly discovered m6A-binding protein, can affect fibrosis by indirectly regulating the lactylation process. Mechanistically, IGF2BP2 enhances the expression of the key glycolytic enzyme ALDOA, thereby promoting glycolytic metabolism and lactate production in human HSCs and mouse livers, which in turn induces H3K18 lactylation and ultimately regulates the fibrotic process [85]. The latest research indicates that overtraining may be a potential risk factor for inducing liver fibrosis [86]. The study revealed that overtraining leads to lactate accumulation in skeletal muscle tissue of mice. These lactates induce lactylation of the SORBS3 protein and activate its liquid-liquid phase separation, thereby promoting the sorting of FBXO2 into lactate bodies. These lactate bodies, isolated from overtrained mice or lactate-stimulated C2C12 cells, induce hepatocyte apoptosis and activate HSCs, ultimately triggering liver fibrosis through a dual mechanism [86].

Lactylation in pulmonary fibrosis

In pulmonary fibrosis, TGF-β1 and IL-1β synergistically activate lung fibroblasts, enhancing glycolysis to produce excessive lactate, which in turn induces histone lactylation and promotes the expression of profibrotic genes (such as α-SMA and collagen I). Activation of the GLP-1 receptor alleviates pulmonary fibrosis by inhibiting glycolysis and the NLRP3 inflammasome in primary mouse lung fibroblasts, thereby reducing lactate production and histone lactylation [87]. Interestingly, a similar mechanism is also observed in crystalline silica (CS)-induced pulmonary fibrosis models: CS exposure induces metabolic reprogramming in mouse alveolar macrophages, which then activates the NLRP3 inflammasome through histone lactylation, promoting the secretion of inflammatory factors and ultimately leading to pulmonary fibrosis [88]. In arsenic-induced pulmonary fibrosis models in mice, lactylation regulates the expression of H3K18 and YTHDF1, affecting the stability of m6A-modified NREP mRNA and thereby modulating the expression level of TGF-β1 to promote fibrosis [89]. Moreover, lactate can induce the expression of profibrotic genes such as ARG1 and PDGFA in mouse alveolar macrophages through lactylation, enhancing their profibrotic activity [73]. Similarly, in mouse models of PM2.5-induced pulmonary fibrosis models, lactylation prompts macrophages to secrete more profibrotic factors, exacerbating the fibrotic process through the TGF-β/Smad and VEGFA/ERK signaling pathways. The LDHA inhibitor GNE-140 can effectively reduce the degree of fibrosis [90].

Lactylation in renal fibrosis

In renal fibrosis, EMT is one of the key mechanisms. Tubular epithelial cells (TECs) promote the progression of EMT and affect kidney function by secreting pro-inflammatory factors such as TGF-β and TNF-α. Recent studies have confirmed that lactylation is also involved in the above processes. Xiang et al. found that increased expression of pyruvate kinase M2 in mouse renal TECs leads to increased lactate production. Lactate induces histone H3K18 lactylation to accumulate in the TGF-β1 gene promoter region, thereby promoting TGF-β1 expression and driving the transformation of mouse M2 macrophages into myofibroblasts, exacerbating renal fibrosis [74]. In addition, mouse podocytes stimulated by high glucose enhance the transcriptional activity of glycolysis-related genes by enriching lactylation in their promoter regions, thereby promoting EMT in podocytes [34]. Moreover, in diabetic nephropathy models, elevated

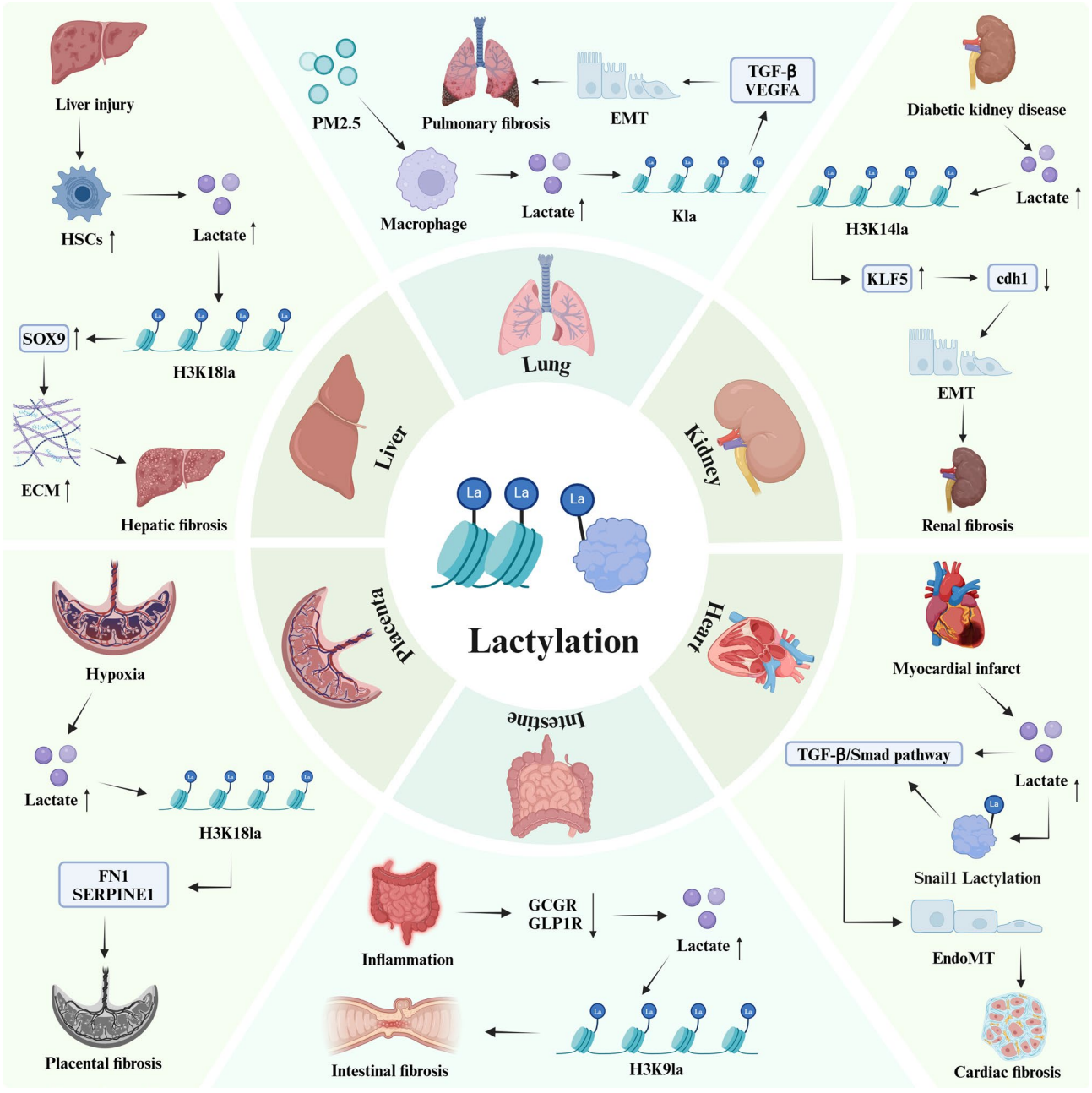

Fig. 3 Schematic diagram of the molecular mechanisms of lactylation modification in organ fibrosis. Emerging evidence highlights multiple Kla-related pathological pathways in fibrosis: In the liver, tissue injury induces HSCs activation, which upregulates SOX9 expression via H3K18la to accelerate liver fibrosis. In the lung, Kla promotes macrophages to secrete pro-fibrotic factors, leading to pulmonary fibrosis through EMT. In the kidney, elevated H3K14la levels drive EMT in renal cells, contributing to renal fibrosis. In the heart, lactylation of Snail1 activates the TGF-β/Smad2 pathway, inducing EndoMT. In the intestine, inflammatory responses downregulate GCGR and GLP1R expression, driving H3K9la-mediated intestinal fibrosis. In the placenta, H3K18la enhances the expression of fibrotic factors such as FN1 and SERPINE1. (Abbreviations: cdh1 cadherin 1; ECM extracellular matrix; EMT epithelial-mesenchymal transition; EndoMT endothelial-to-mesenchymal transition; FN1 fibronectin 1; GCGR glucagon receptor; GLP1R glucagon-like peptide 1 receptor; HSC hepatic stellate cell; KLF5 kruppel-like factor 5; SERPINE1 serpin family E member 1; SOX9 SRY-associated high mobility group box; VEGFA vascular endothelial growth factor A)

lactate levels in renal TECs (HK-2 and mTECs) promote the formation of H3K14la, which activates the expression of the KLF5 transcription factor. KLF5 then binds to the promoter region of the cdh1 gene in HK-2 cells and inhibits its transcription, ultimately accelerating EMT in renal tubular epithelial cells [91].

Table 2 Therapeutic strategies targeting lactylation in fibrosis

Organ	Drug	Study Type	Target	Function	Ref
Liver	DCA	Preclinical	PDHK	Reduced the levels of lactate and H3K18la	[81]
	2-DG	Preclinical	Undefined	Decreased H3K18la levels and inhibited the activation of HSCs	[85]
	Salidroside	Preclinical	LDH	Reduced lactate bodies and mitigated hepatocyte apoptosis	[86]
Lung	liraglutide	Preclinical	GLP-1R	Inhibited histone lactylation induced by TGF-β1 and IL-1β	[87]
	2-DG	Preclinical	Undefined	Inhibited the activation of the NLRP3 inflammasome and pyroptosis	[88]
	α-CHCA	Preclinical	MCT1	Inhibited the transcription of YTHDF1 and the m6A modification of NREP	[89]
	AF12198	Preclinical	IL-1	Inhibited the phosphorylation and activation of NF-κB	[107]
	GNE-140	Preclinical	LDHA	Reduction of H3K18la decreased the expression of fibrosis-promoting genes	[90]
Kidney	DCA	Preclinical	Undefined	Decreased the expression of H3K18lac and pan-Kla	[108]
	Shikonin	Preclinical	PKM2	Inhibition of histone lactylation and TGF-β1 expression	[74]
	Ox	Preclinical	LDHA	Reduction of H3K14la and the expression of KLF5	[91]
	Ox	Preclinical	LDHA	Alleviated the formation of podocyte EMT	[34]
	FX-11	Preclinical	LDHA	Decrease the level of H3K18la	[109]
	3PO	Preclinical	PFKFB3	Decreased H4K12la levels and suppressed NF-κB signaling pathway activation	[110]
Heart	CHC	Preclinical	MCT	Inhibition of lactate-induced Snail1 lactylation and acetylation	[93]
Intestine	1907B	Preclinical	GCGR/GLP1R	Decreased the level of H3K9la	[94]
Spinal Cord	4-CIN	Preclinical	MCT	Reduced the level of H4K12la	[111]
Flap	CHC	Preclinical	MCT	Reduced the lactylation and acetylation of Twist1	[67]
Peritoneum	oxamax	Preclinical	Undefined	Reduced the expression of senescence and fibrosis markers	[95]

Note: Classification of study type is based on experimental model. "Preclinical" includes studies based on animal models and in vitro systems (including human cell lines). "Undefined" indicates that the referenced study did not specify a direct molecular target such as enzymes, cytokines, receptors, or channels.

Abbreviations: 2-DG 2-Deoxy-D-Glucose; 3PO 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one; 4-CIN&CHCα-cyano-4-hydroxycinnamate; DCA dichloroacetate; GLP-1R glucagon-like peptide 1 receptor; HSCs hepatic stellate cells; IL-1 interleukin-1; KLF5 kruppel-like factor 5; LDH lactate dehydrogenase; MCT monocarboxylat transporter; NF-κB nuclear factor-κB; NLRP3 NACHT, LRR and PYD domains-containing protein 3; NREP neuronal protein; Ox oxamate; PFKFB3 6-Phosphofructo-2-kinase/Fructose-2,6-biphosphatase 3; PKM2 pyruvate kinase M2; YTHDF1 YTH domain family protein 1; α-CHCAα-Cyano-4-hydroxycinnamic acid.

Lactylation in fibrosis of other organs

Cardiac fibrosis is a major pathological process following myocardial infarction, and excessive cardiac fibrosis reduces cardiac compliance and ultimately leads to heart failure [92]. The TGF-β/Smad pathway plays an important role in the fibrotic process. Studies have found that lactylated transcription factor Snail1 in human endothelial cells upregulates the expression of the TGF-β/Smad2 pathway through a nuclear translocation mechanism, thereby activating EndoMT and exacerbating cardiac fibrosis in myocardial infarction mouse models [93]. In addition, there is convincing evidence that lactylation plays a role in fibrosis of the intestines, peritoneum, and placenta. In Crohn's disease patients and mouse models of chronic colitis, downregulation of intestinal GCGR and GLP1R expression leads to abnormal accumulation of lactate, which induces lactylation of histone H3 at the K9 site and exacerbates intestinal fibrosis through EMT [94]. In peritoneal fibrosis research, high-glucose peritoneal dialysis fluid induces H3K18 lactylation in peritoneal mesothelial cells in mice, thereby promoting peritoneal mesothelial cells senescence and worsening peritoneal fibrosis [95]. Li et al. found that in preeclampsia, decreased uteroplacental blood flow stimulates increased lactate production in human placental trophoblasts, which in turn induces histone lactylation and ultimately affects the fibrotic process in the placenta by regulating the expression of fibrosis-related genes (FN1 and SERPINE1) [96]. The above research results collectively reveal the key regulatory role of lactylation modifications in organ fibrosis (Fig. 3).

Potential lactylation-based drugs and therapeutic strategies

Lactylation plays a key driving role in the fibrotic process by regulating core biological processes such as extracellular matrix remodeling, inflammatory responses, and metabolic reprogramming. With in-depth research into the molecular mechanisms of lactylation-driven fibrosis, innovative therapeutic strategies based on lactylation regulation show great clinical application potential. Table 2 summarizes the fibrosis-treating drugs developed based on the currently discovered lactylation mechanisms.

Conclusion and prospect

Lactate and its newly discovered post-translational modification, lactylation, play a key role in fibrosis. Lactate is not only a product of metabolic reprogramming but also regulates cell signaling, the immune microenvironment, and extracellular matrix remodeling, thereby playing an important role in the occurrence and development of fibrosis. Lactylation, as an emerging protein modification, provides a new perspective for elucidating the multiple biological functions of lactate. This modification is involved in gene expression regulation networks by altering the modification states of histones and non-histone

proteins, thereby affecting cell function reprogramming. This review systematically explores the latest literature, highlighting the mechanisms and applications of lactate and lactylation in fibrosis progression. It provides a new perspective for understanding the pathogenesis of fibrosis and offers new directions for the development of novel therapeutic strategies.

Although the progress in the functions and mechanisms of lactate and lactylation has brought new hope for the diagnosis and treatment of fibrosis, the exact molecular mechanisms by which lactate and lactylation affect fibrosis are still directions that need to be deeply investigated in the future. Previous studies have shown that a variety of immune cells and their related signaling pathways play key roles in the fibrotic process [97]. Further elucidation of the regulatory mechanisms of lactate metabolism on the immune microenvironment will become an important direction for future research. In addition, there is a complex interaction network between lactylation and other PTMs [45]. In-depth research on the cross-linking mechanisms between lactylation and other PTMs will help to fully understand the molecular mechanisms of fibrosis and identify new therapeutic targets. In particular, the enzyme responsible for catalyzing lactylation, often referred to as putative lactyltransferases, have not yet been clearly identified. This represents a significant mechanistic gap, and further research is needed to uncover the enzymatic machinery and its regulatory networks. Understanding these mechanisms may offer new opportunities for therapeutic intervention, although such strategies are currently speculative and require cautious interpretation. Lactate, as an important metabolic biomarker, is closely related to the prognosis of many diseases [98–101]. Based on the technological innovation of novel lactate dynamic sensors [102], it is hoped that the precise mapping of lactate dynamic metabolism during the fibrotic process can be achieved. From a translational perspective, all antifibrotic agents targeting lactylation modification discussed in this review remain in the preclinical research stage. While these compounds have shown promising results in animal models and in vitro systems, their clinical relevance and therapeutic efficacy in humans are yet to be determined. Future studies should prioritize early-phase clinical trials and the development of lactate-sensitive biomarkers to stratify patients and monitor treatment responses. In summary, the role mechanisms of lactate metabolism and its lactylation modifications in fibrosis are a highly promising but still underdeveloped research field. In-depth research is expected to bring new breakthroughs to the diagnosis and treatment of fibrotic diseases.

Abbreviations

CBP	Creb-binding protein
CS	Crystalline silica
ECM	Extracellular matrix
EndoMT	Endothelial-to-mesenchymal transition
EMT	Epithelial-mesenchymal transition
GLO1&2	Glyoxalase 1&2
HSCs	Hepatic stellate cells
Kla	Lysine lactylation
LDH	Lactate dehydrogenase
LGSH	Lactoylglutathione
LPS	Lipopolysaccharide
MCT	Monocarboxylate transporter
MGO	Methylglyoxal
PTM	Post-translational modification
TECs	Tubular epithelial cells

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Data availability
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Declarations

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